Water Conservation and Re-use in The Pharmaceutical Biopharmaceutical Industry

Business Perspective, Opportunities and Examples

Ed Helmig,

Principal Project Engineer

Wyeth BioPharma

Presentation Agenda
Water Conservation and Re-use

- **Business Perspective- *Pharmaceuticals and Biotechnology***
- **Wyeth BioPharma: Business Overview**
- **BioPharma Production Technology**
- **Purified Water Systems**

Water Conservation and Recovery/Re-use: tools and examples.

- General Approach
- Specific Examples
- Risk Factors

Membrane Technology

Example #1: Combined MBR+Ozone Technology for Effluent Recovery and Re-use.

Example #2: Pollution Prevention at a Vaccine Production Facility- handout.

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Water Conservation and Reuse

Business Perspective- Pharmaceuticals and Biotechnology

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US Market Leaders- Pharmaceuticals

Revenue figures (2005) are in billions $

- Pfizer ($51.3)
- Johnson and Johnson ($50.5)
- Abbott ($22.3)
- Merck ($22.01)
- Bristol-Meyers Squibb ($20.2)
- Wyeth ($18.7)
- Eli Lilly ($14.6)
- Amgen ($12.4)
- Schering-Plough ($9.5)
- Forest Laboratories ($3.1)

Source: CNN/ Money/ Fortune 500, 2006

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Market Leaders (2005) - Global Biopharmaceuticals

Revenue (2004) figures are in billions (4)

- Amgen ($9.9)
- Genentech ($3.7)
- Serono ($2.17)
- Biogen Idec ($2.11)
- Genzyme ($1.47)
- Gilead ($1.24)
- Medimmune ($1.12)
- Chiron ($0.99)
- Millennium ($0.35)
- Intermune ($0.147)

Source: *Contract Pharma*

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Biotechnology Business in Massachusetts

- **254 Companies Listed in The Massachusetts(MA) Biotechnology Industry Directory!**
- **Some key players in MA Market:**
  - Abbott
  - Amgen
  - AstraZeneca
  - Genzyme Corp
  - Millennium Pharmaceuticals Inc.
  - Novartis
  - Pfizer
  - Sanofi Aventis
  - Serono
  - **Wyeth BioPharma**

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Global Biopharmaceutical Market Profile

- 2004 Revenues: $45 Billion dollars (15-17% revenue growth in 2004)
- 2011 Revenue forecast: $92 Billion
- Average annual growth rate (2004-2011): 10.3%
- Current US Market Share: 60% of global market.

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Locations and Profiles

Major Sites

- **Andover MA (USA**): 1.1 Million sq ft, $800M investment. Capabilities- Commercial Drug Substance, Pilot, Product and Process Development, Pilot Lab, Clinical Drug Substance and Product, Clinical Fill and Finish, Quality and Site Support. Key Products: ReFacto, BeneFix, Mylotarg.
- **Algete (Spain):** small facility that manufactures Varidase and does fill and finish work for various products including BeneFix, ReFacto, Dimethicone, and the antibiotic Erythomycin.
- **Grange Castle Ireland** (*Worlds largest integrated biotech facility*)- 1.2 million sq ft, $2 billion investment, projected revenues 4 billion/yr by 2007. Capabilities: Commercial Drug Substance, Pilot (approved 2006) and Product and Process Development Labs. Key products- Enbrel, Tygacil, Prevnar (13 valent).
- **Pearl River NY (USA):** 400,000 sq. ft. plant primarily devoted tp Prevnar conjugation step (adds polysaccharides to carrier protein) and Vaccine research.
- **Sanford NC (USA):** > 1MM sq ft. Manufacturing Facility and Vaccine Development. Products: Prevnar carrier protein, HibTitter, Meningeococcal Conjugate, and CRM_{197} carrier protein.

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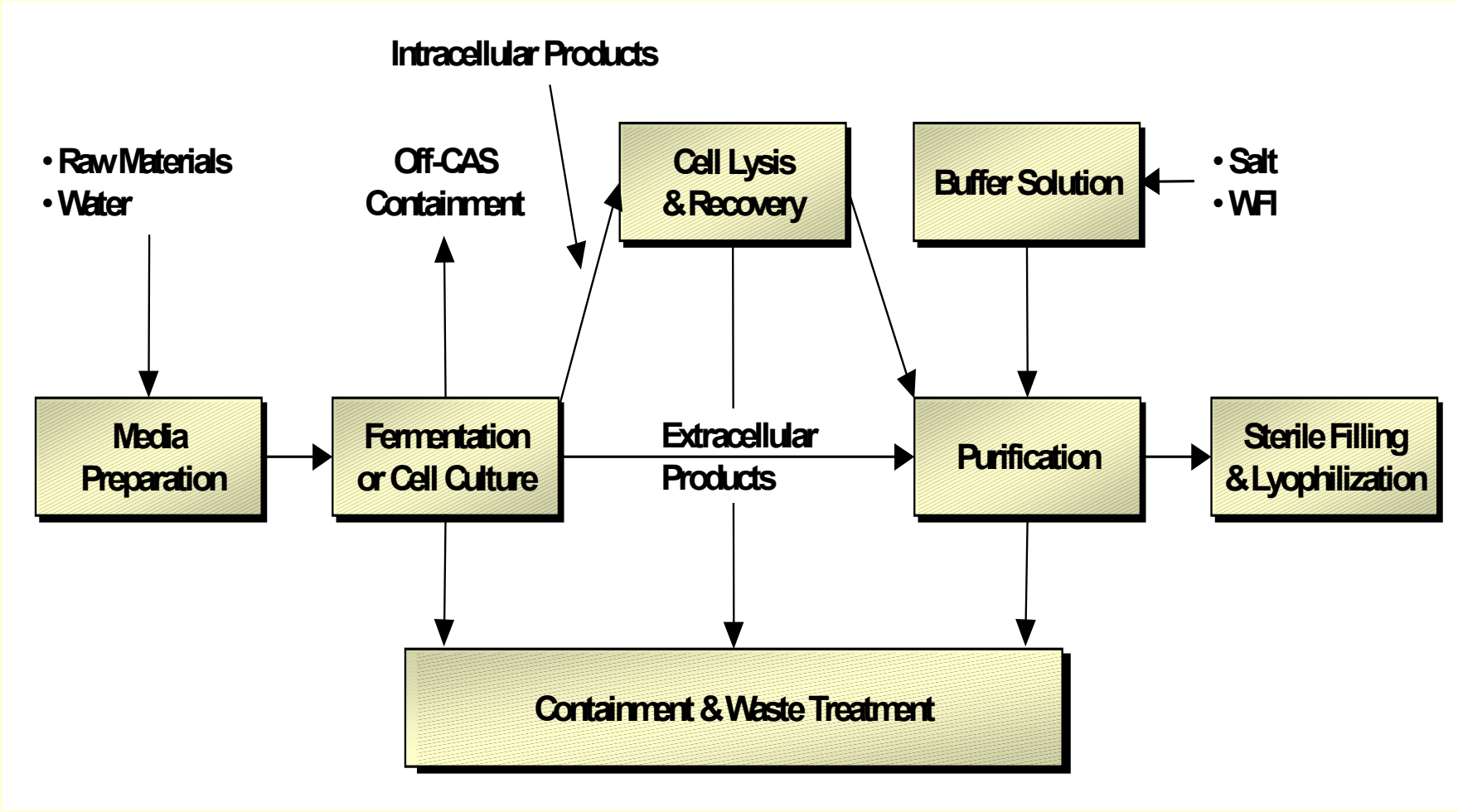
Typical BioPharma Production Process-Simplified



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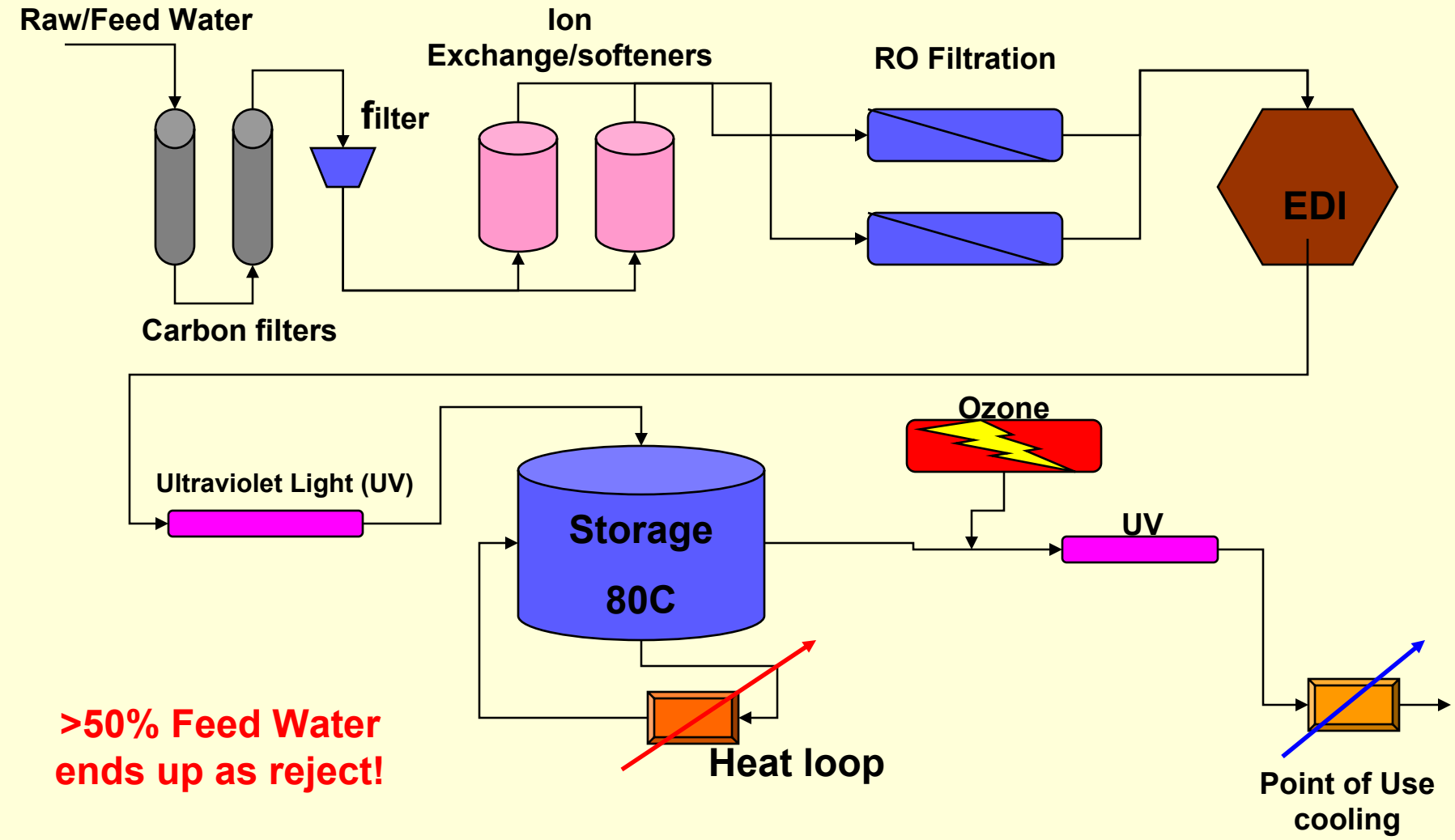
Typical USP/WFI Water System

Simplified version of Wyeth Newbridge System



>50% Feed Water ends up as reject!

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Typical BioPharma Pilot Facility

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Water/Wastewater Management
How it effects the business

- **Compliance**
  - FDA (USP 23)
  - EPA
  - Local POTWs
  - Receiving streams
- **Cost of Goods Sold**
  - Infrastructure & site complexity
  - Energy and Chemicals
  - Manpower
  - Disposal of by products- sludge's and biosolids
- **Public Health and Environment**
  - Water quality in receiving stream
  - Public Relations

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The Business Perspective
Water/Wastewater Management

- **Water is one of the most important resources used in the production of Pharmaceuticals.**
  - Large amounts of Purified (USP Grade) water is **used in production** and equipment cleaning
  - Softened water is used in boilers and cooling towers for both process and building heating and cooling
  - Tap water is used by employees and contractors
- **Water Usage & Cost at Wyeth (2003- 67 Sites)**
  - 3.56 Billion Gallons– $6.85 Million
- **Wastewater Discharged & Costs (2003- 67 Sites)**
  - 2.07 Billion Gallons- $11.6 Million

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Cost/Business Perspective

Estimated Range of Water/Wastewater Management Costs.

Potable Water:

Range = 2- 8 $/1000gal

Mean ~ 4- 6 $/1000 gal

Purified Water (USP Grade): 20-60 $/1000 gal

Reported Wastewater Management Costs[1]:

- **Major Pharma[2] Production Sites**:
  - Range: 2 - 22 $/1000gal
- **Major Nutri Production Sites:**
  - Range: 4 - 37 $/1000 gal
- **Major Vaccine Production Sites**
  - >1- 39 $/1000 gal.

Footnote 1: Source data is 2003 PARS Report. Data is subject to reporting errors re. inclusion/exclusion of sludge disposal costs, costs for power, and cost for other on site treatment systems. Wide range of costs are related to (1) nature of discharge (direct/indirect), (2) license/pretreatment requirements, (3) volume/economics of scale and (4) end use (discharge vs. reuse).

Footnote 2: Includes estimated cost for new WWTP in Newbridge.

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Business Perspective
Cost for Water/Wastewater

Estimated total cost for water/wastewater infrastructure and management is about 0.2- 0.3% of the Cost of Good Sold (CGS)

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Typical Range of Wyeth Capital Expenditures for Water and Wastewater Treatment Systems

- **USP/WFI Generation System: 1.2 - 4.0 MM** (does not include distribution)
- **Small pH System: $ 0.5 MM**
- **Nutritional WW Treatment System: $4 -12 MM**
- **Vaccine WW Treatment System: $2 - 5 MM**
- **Pharmaceutical WW Treatment System: $10 - 30 MM**

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Greenfield Sites/New Construction

- **Budget** 2 – 4 % of Total Capital Cost for Water and Wastewater Infrastructure **!**
- **Cycle Time –**New WWTP Design & Construction:
  - **1.5 – 2 yrs (Standard WWTP)**
  - **3- 4 yrs for Novel/High Tech WWTP involving bench and pilot studies and long lead/custom fabricated equipment.**

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Bottom Line

- Water and wastewater issues effect the sustainability of the Pharmaceutical and Biopharmaceutical Industry in the US and The State of Massachusetts.
- A water shortage or serious decline in water quality would affect business and industry.
- The availability, reliability, and capacity of Municipal water supplies and wastewater treatment facilities are considerations in citing new Pharma and BioPharma facilities and sustaining both the R&D and Manufacturing aspects of the business.
- Wyeth has abandoned major site expansion plans in locations where water supplies could not be guaranteed!

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Water Conservation/Recovery and Re-use

Principles and Tools for Industry Based on Real-World Experience at Wyeth

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First Step

Conduct a

Water Conservation Opportunity Assessment

at your site!

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Principles and Tools
Industrial Facility Water Conservation, Recovery and Re-use

Construct:

- Water/Wastewater Balance for your site

Evaluate:

- Water/Wastewater Characteristics
- Consider heat sources and sinks
- Effluent re-use options and risks.
- Costs and Return on Investment (ROI)

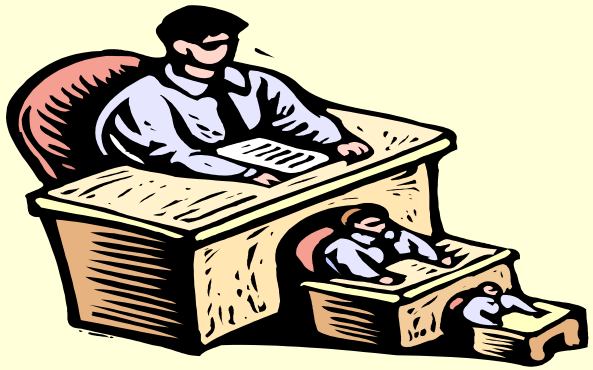
Identify:

- Major Points of Use and Water Quality Requirements
- Materials of construction (MOC) issues and equipment tolerances

Principles and Tools
Industrial Facility Water Conservation, Recovery and Re-use

Communicate:

- Water conservation goals and practices should be communicated to employees and most importantly the Sites Engineering, EHS, Maintenance and Utilities Groups.
- Engage all departments at the site in a **Water Conservation Opportunity Assessment Program**. Consider and *Ideas in The Workplace Type Program* with recognition and rewards.



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Major Targets for Water Usage/Conservation and Re-use

- **Cooling Towers-** max out cycles of concentration to minimize make-up water requirements**.** Ozone treatment plus side stream filtration can be used to enable a C/T to run at up to 20 cycles of concentration.
- **Point of Use Coolers (USP Water Systems with hot water storage distribution loops):** eliminate once thru non contact cooling water- tie coolers into a closed loop chiller.
- **Pump Seal Water-** collect and re-use or change out pumps to variety with mechanical seal.
- **RO Systems:** minimize reject volume by frequent cleaning. Consider re-use of RO reject (typically 25% of feed) in cooling towers.

Major Targets for Water Usage/Conservation and Re-use

- **AHU Condensate:** collect and re-use.
- **Still Blow-down:** evaluate for heat recovery and re-use.
- **Softeners:** examine and replace resins per manufacturers recommendations (based on damage by fouling, oxidation, deformation and/or useful life). Upgrade system if appropriate. Automate regeneration and backwash cycles based on conductivity break-thru instead of cumulative thru-put.
- **EDR/EDI Reject:** evaluate for re-use.
- **Glassware Washers:** evaluate and replace older units with more water/energy efficient units.

Major Targets for Water Usage/Conservation and Re-use

- **Steam Condensate:** evaluate for heat recovery and re-use.
- **Wastewater- final site effluent**: consider treatment system upgrades to enable re-use. Typically tertiary filtration and disinfection (ozone or UV) is all that is required to produce a re-useable effluent. Reuse options include:
  - **Make-up water for Cooling towers**
  - **Irrigation/Lawn watering (Summer only)**
  - **Groundwater recharge/percolation pond**
  - **Direct discharge to surface water instead of to POTW**

Risk Factors/Impediments to Water/Wastewater Re-use

- **Economics**
- **Perception**
- **Pathogens and related issues** (e.g pathogens could grow and be released in cooling tower drift posing a threat to humans and product)
- **Chlorides:** > 500 ppm can cause Stress Corrosion Cracking (SCC) of Metals. Use of expensive high Nickel/Chromium metals (e.g C-276) are required to avoid SCC.
- **Cross Contamination:** potential for leakage of effluent in shell/tube heat exchangers.
- **Scale, Corrosion and MOC Issues:** need to calculate Langelier Saturation Index and predict impact of water source on scaling and corrosion of equipment.
- **Salt Accumulation** to toxic levels: must be considered in land application cases.
- **Active Pharmaceutical Ingredients (APIs):** must be considered in all cases particularly land and cooling tower applications.
- **Temperature Issues:** blow-down streams are often very hot and must be quenched or cooled before re-use.
- **Vendor Equipment Warranties**

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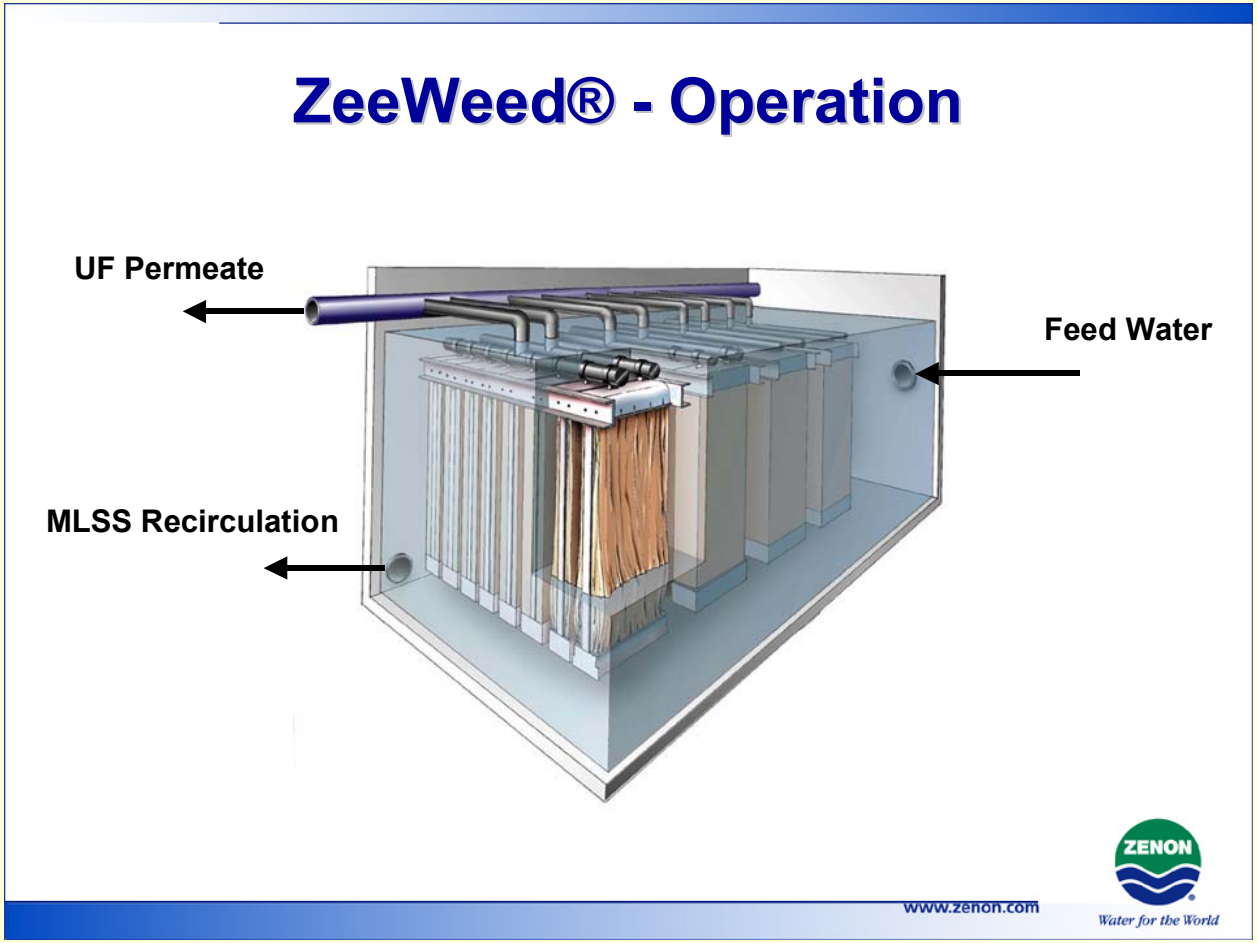
Consider new treatment technologies!
Membrane Bioreactor Concept



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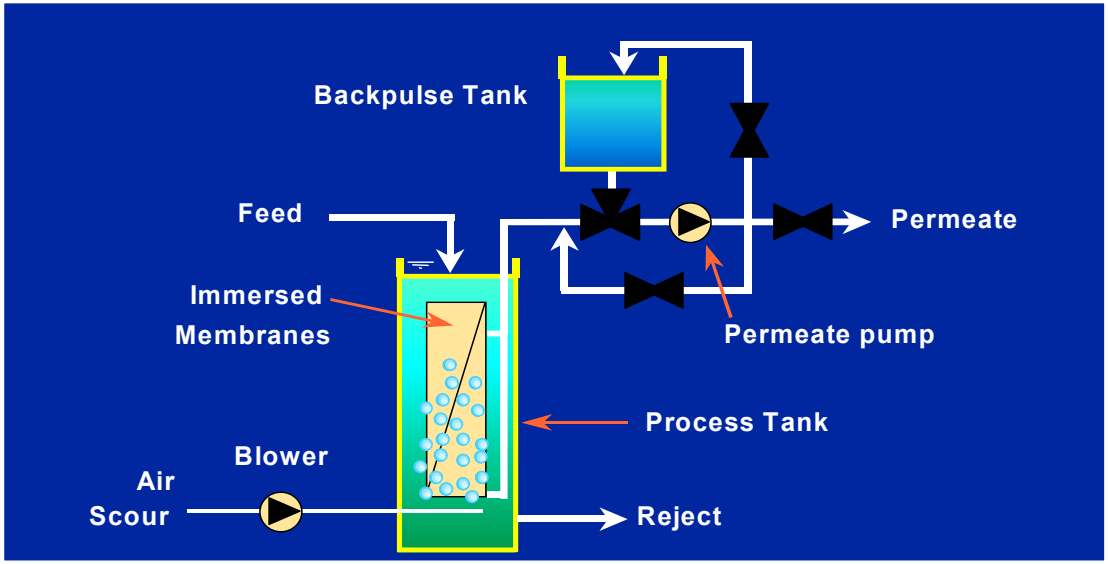
Membrane Bioreactor System

ZeeWeed® UF Process Flow Diagram



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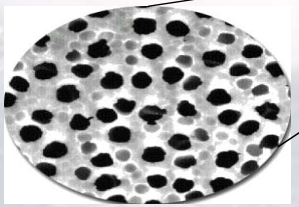
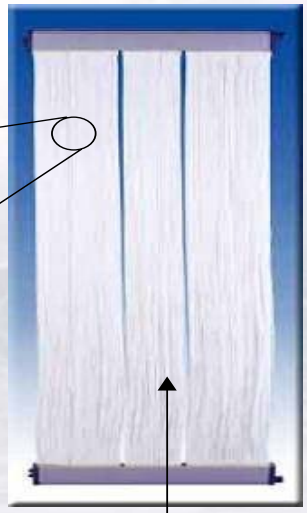
Hollow Fiber Membranes

How Membranes Work



Electron microscope view of membrane surface



ZeeWeed® Membrane Fibers

- Membrane fibers have billions of microscopic pores on the surface
- The pores form a barrier to impurities, while allowing pure water molecules to pass
- Water is drawn through the pores using a gentle suction

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Wyeth Example
Major Pharmaceutical Production Facility- Ireland 2006

Innovative use of Membrane Bioreactor and Ozone Technologies to Produce Re-usable Effluent

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WW Characteristics and Limits – Highlights

Parameter	Influent Ave. (mg/L)	Influent 99th (mg/L)	IPCL Limit (mg/L)	IPCL Limit (kg/day)	Wyeth Targets (mg/L)
Flow (m^3/day)	550	700	--	--	Pending
COD	389	789	2,000	450	<50 - AET
BOD	166	369	800	180	< 5 - AET
TSS	237	480	500	150	< 5 - AET
Total Nitrogen (as N)	18.9	31.2	70	21	< 10 - AET
Ammonia (as N)	8.6	17.4	30	91	< 5 - AET
Total Phosphorus (as P)	6.1	11	20	6	< 7 - AET
pH	2 - 11	--	6 - 9	--	7 - 8
Hormones (each)	**<1-50**		**0.02**	**0.009**	**BDL - AET**
SSRI	**<1-50**		**1**	**0.45**	**BDL - AET**
Tranquilizers (each)	**<1-50**		**0.2**	**0.15**	**BDL - AET**

AET = Achievable Effluent Target
BDL = Below Detection Limit

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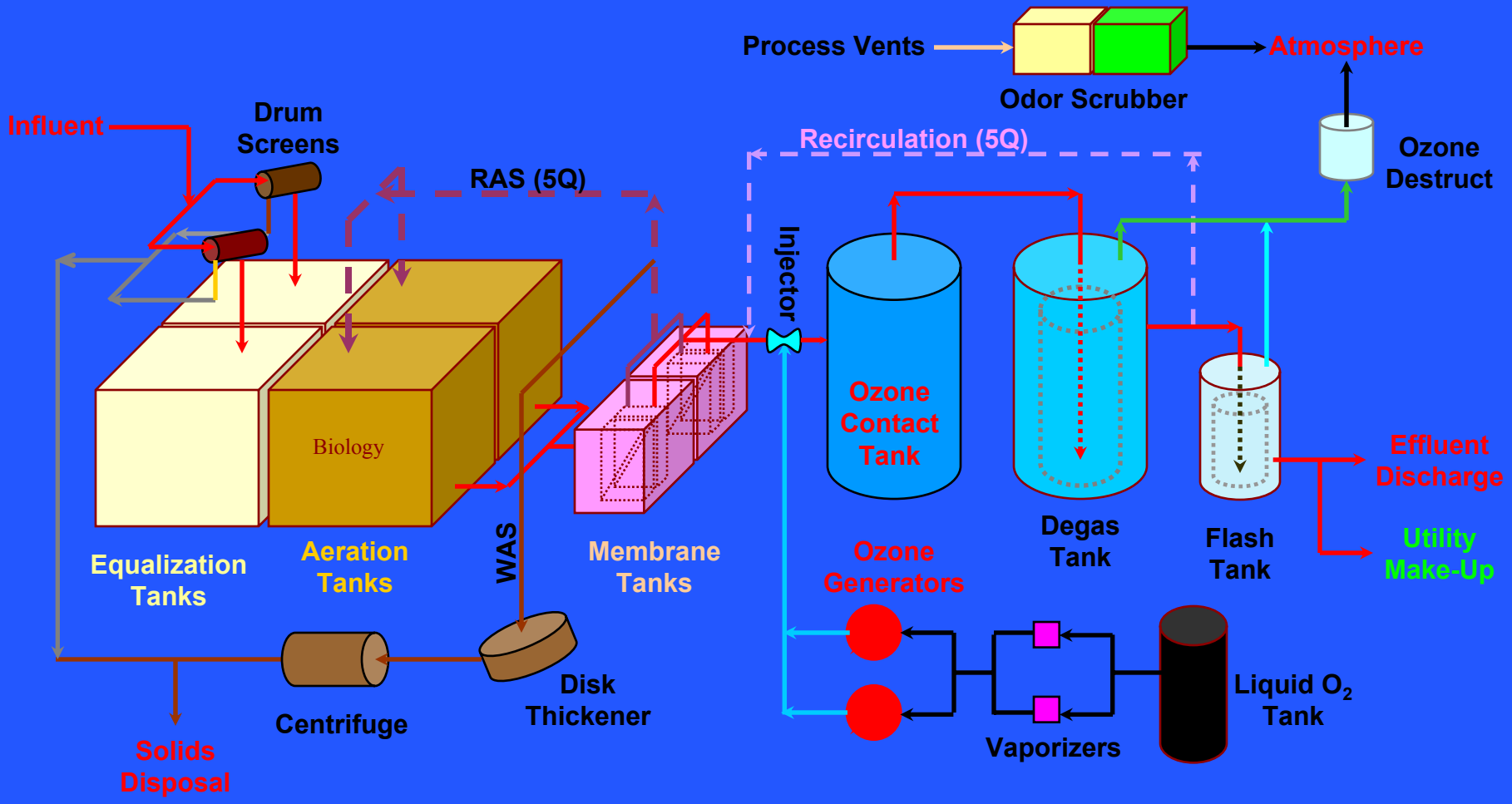
Full Scale Design
Process Flow Diagram (Simplified)



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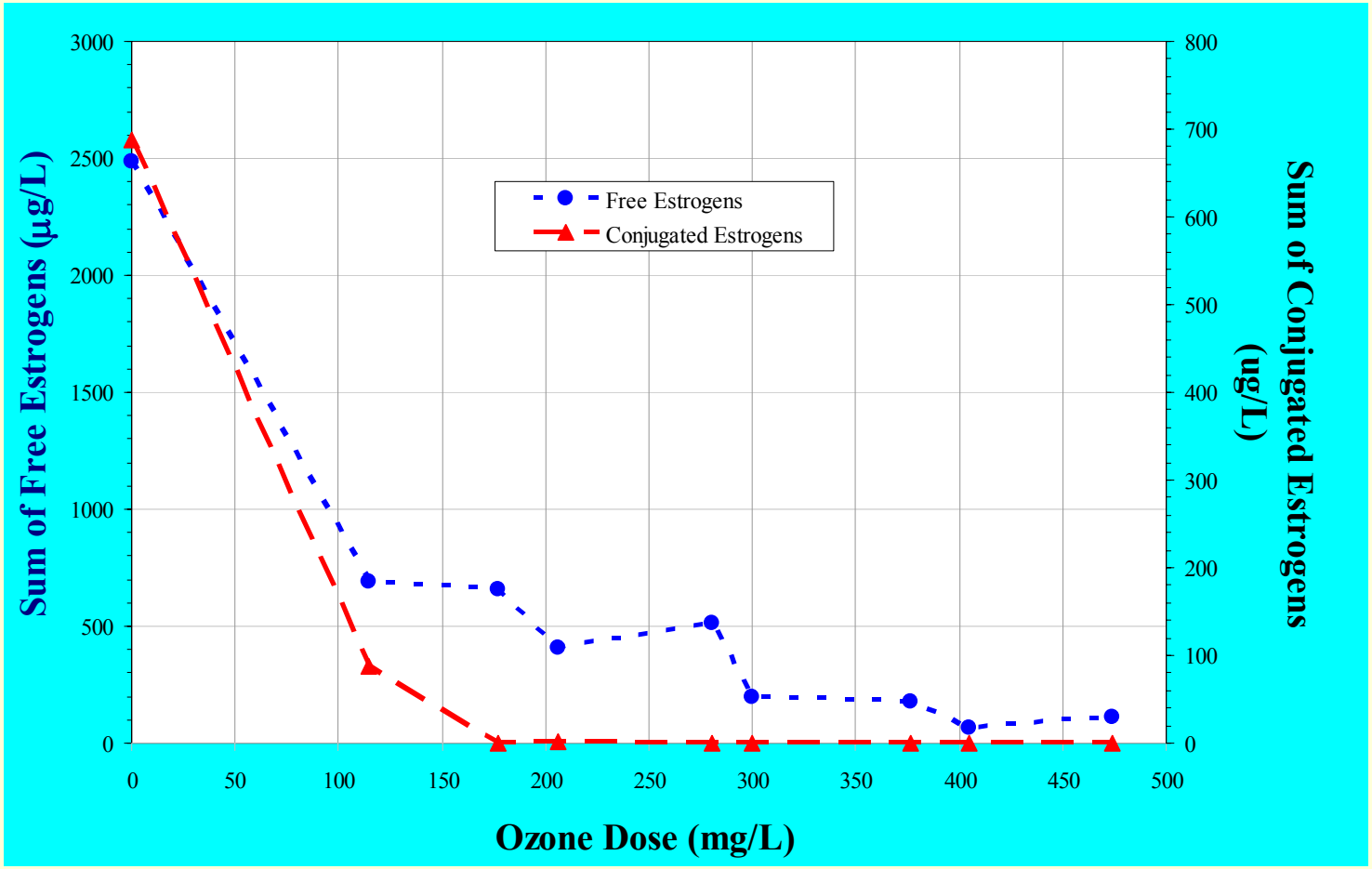
Bench-Scale Ozone Test Results
Cumulative Absorbed Ozone Dosage



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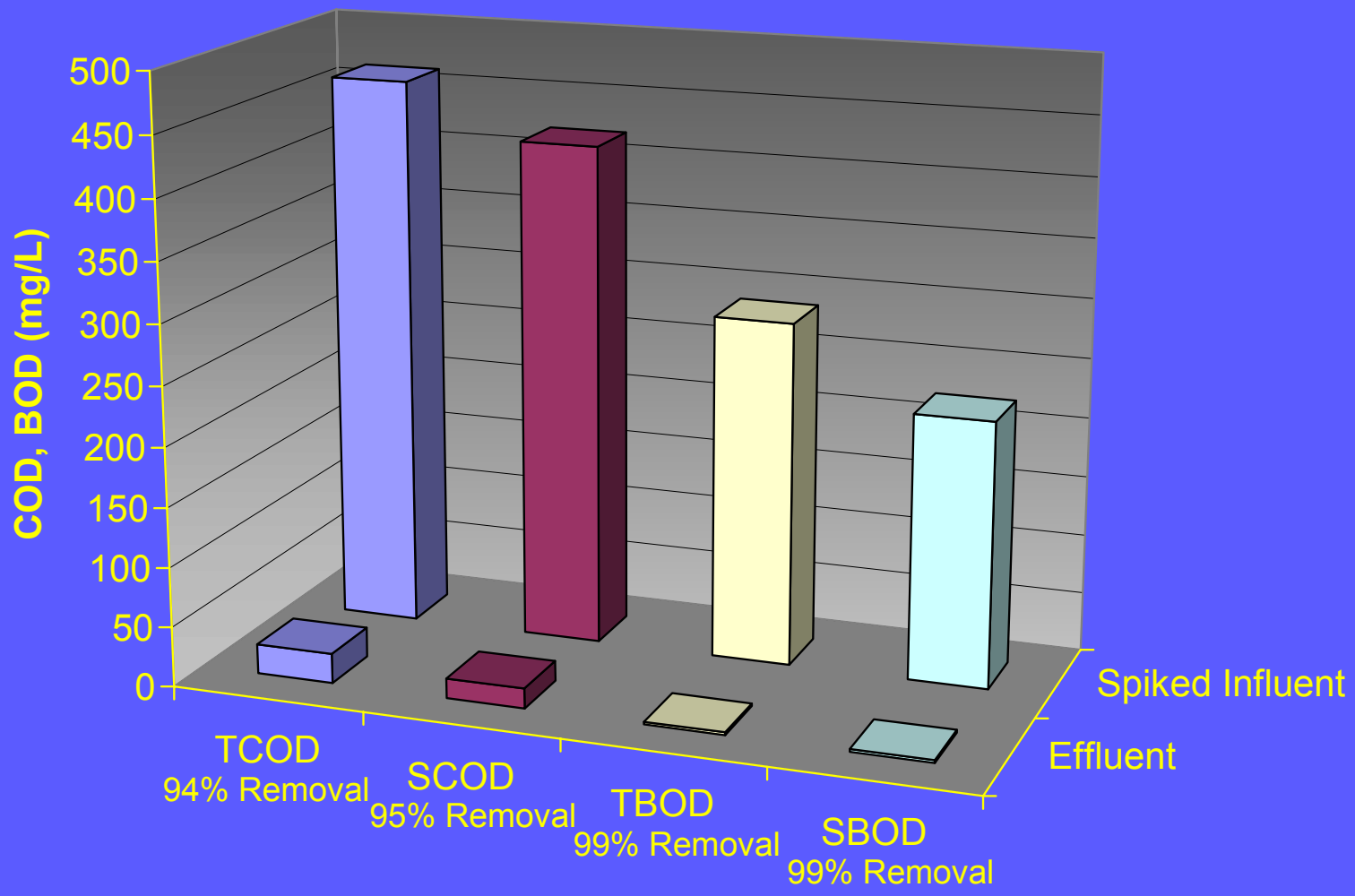
MBR Results – COD and BOD



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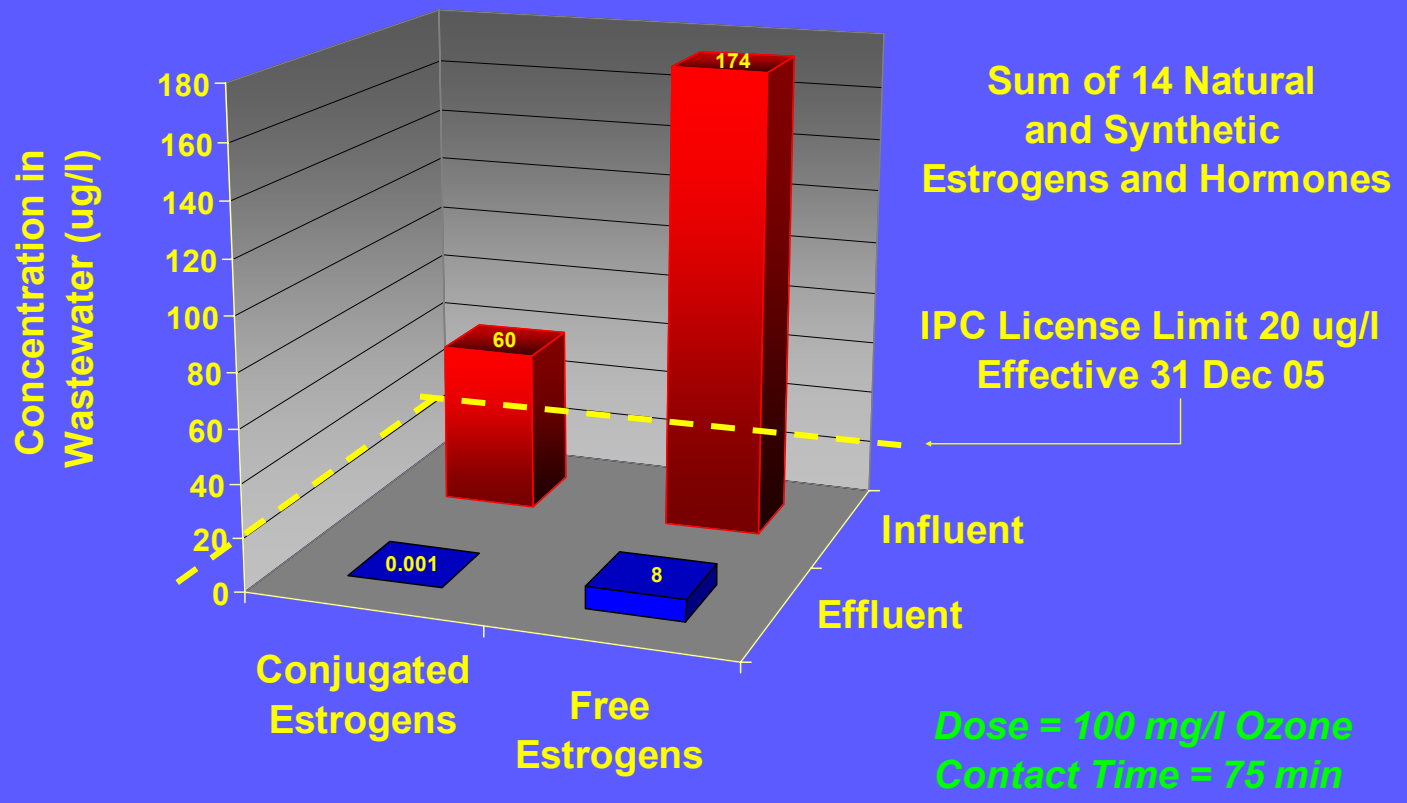
Ozone Destruction of Hormones

Pilot Study- Pharma Plant WW



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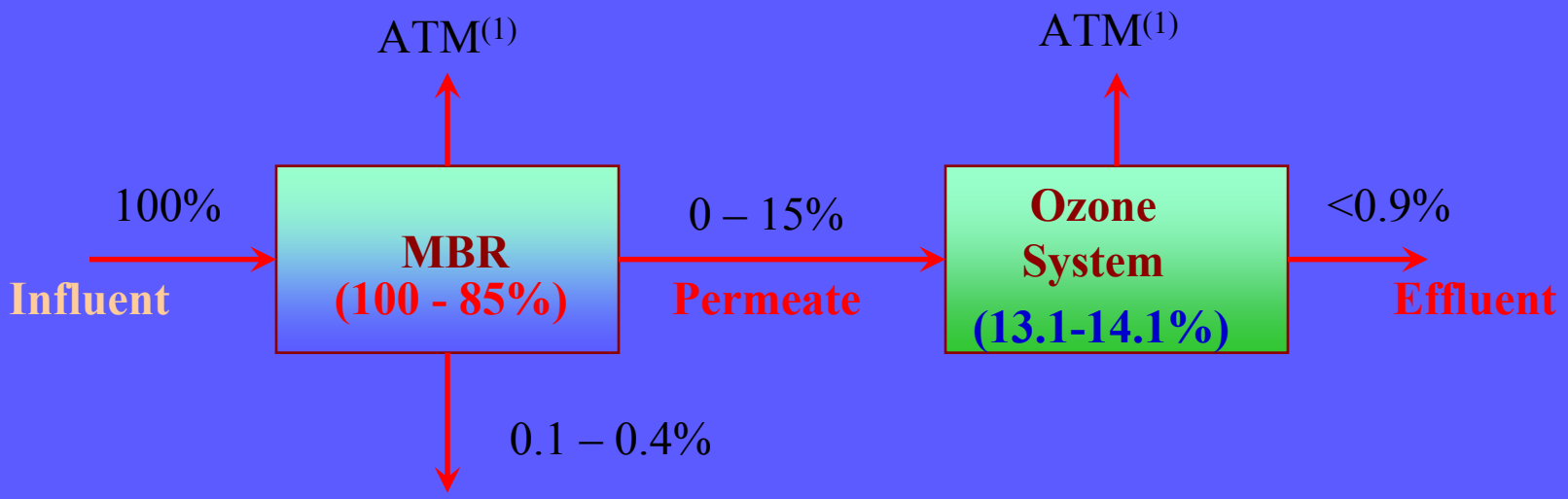
Mass Loading Performance Summary



Note 1: Atmospheric Losses Not Tested
(see Schoenberg et al., Presentation Session 61, 4:00 PM)

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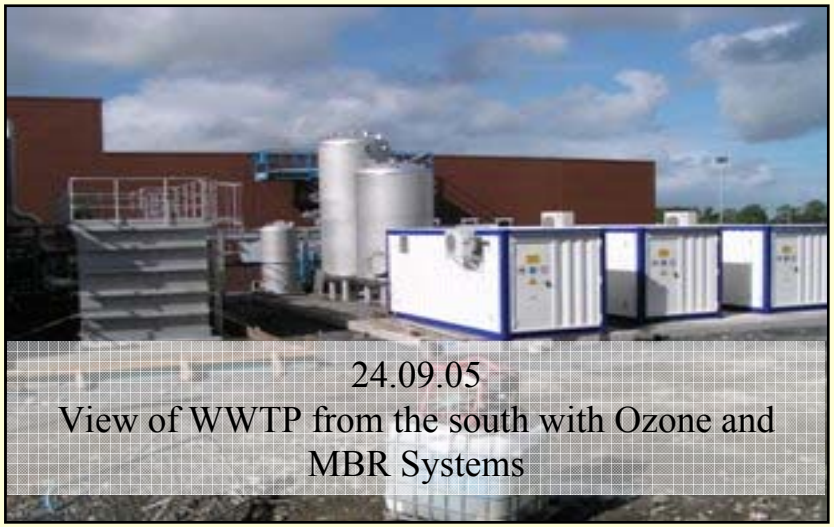
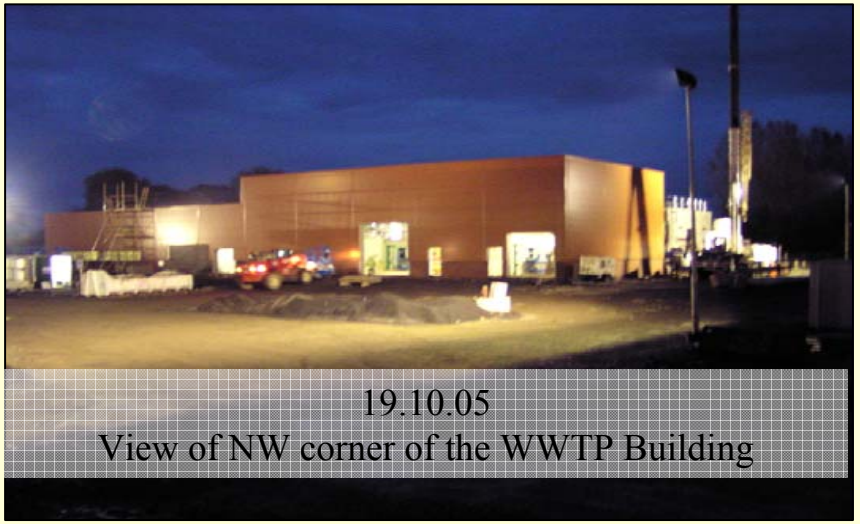
WWTP Construction



24.09.05
View of WWTP from the south with Ozone and MBR Systems



19.10.05
View of NW corner of the WWTP Building

03.10.05
View of NW corner of the WWTP Building

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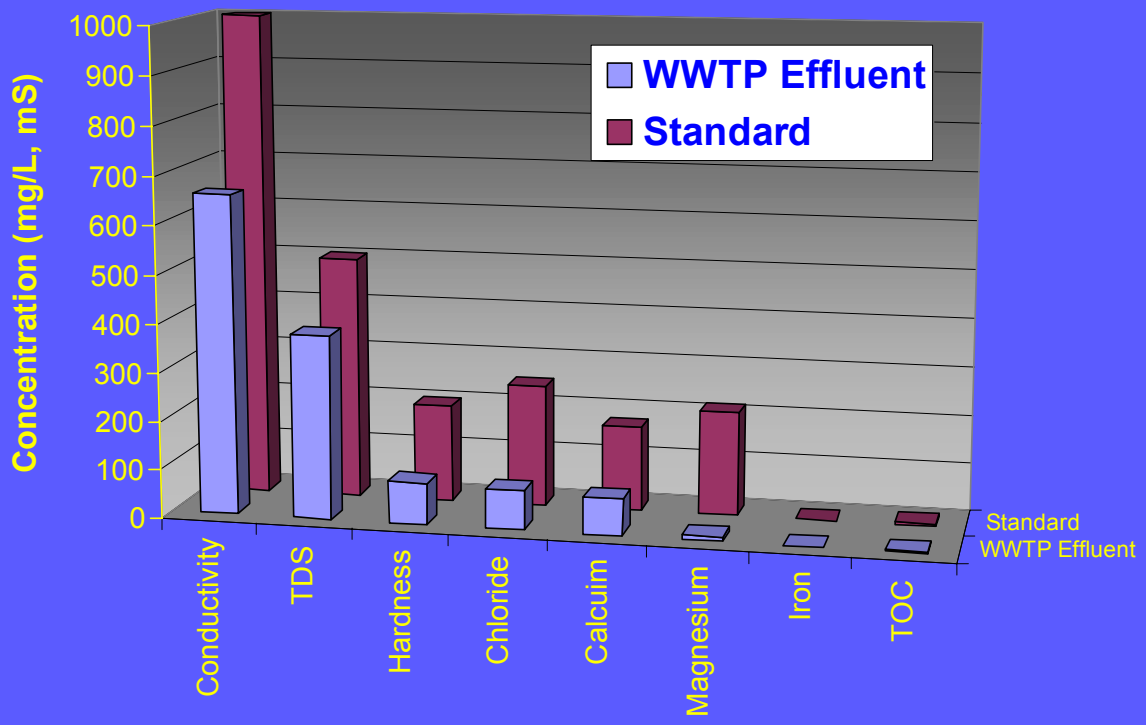
Final Effluent Quality



	Conductivity	TDS	Hardness	Chloride	Calcuim	Magnesium	Iron	TOC
WWTP Effluent	658	380	86	82	76	9.5	0.16	3
Standard	1000	500	200	250	175	215	0.3	5

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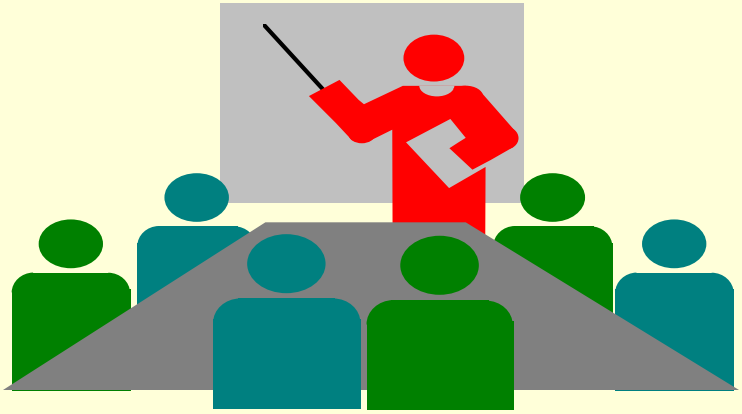
Tip for Regulators

- **Permit Conditions:** Write water conservation/P2 requirements into permits as a condition.
- Irish EPA does this in their Integrated Pollution Prevention and Control Licenses (IPPC). Sites are required to assess water conservation/re-use and other P2 opportunities and give an annual report to EPA on the results of the assessment and their action plan.



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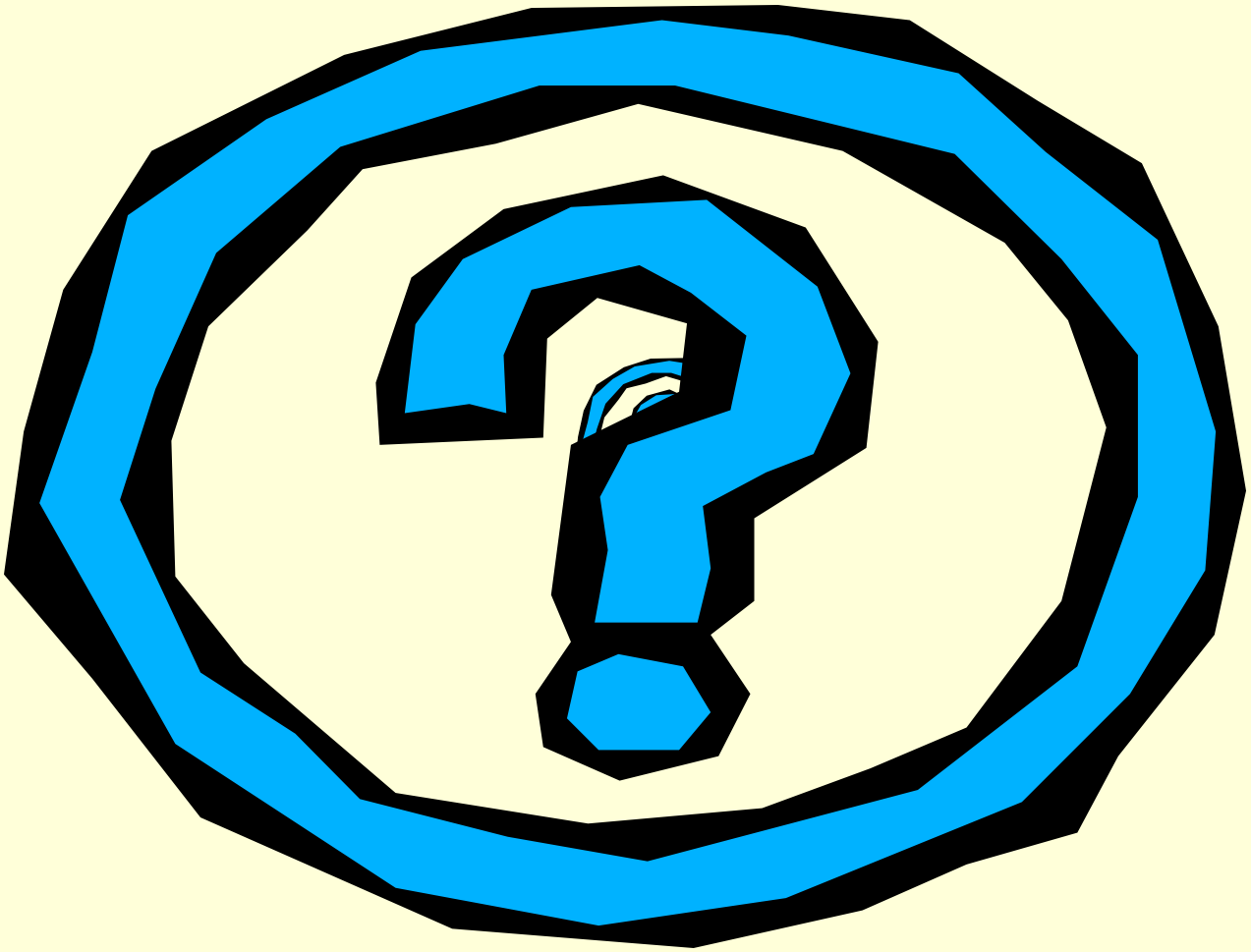
Questions and Answers



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